Characterization and therapeutic potential of induced pluripotent stem cell-derived cardiovascular progenitor cells.

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Public Summary:
Our study shows proof of principal that embryonic stem cells and induced pluripotent stem cells can be driven to make all three cardiovascular (heart cell) lineages in the laboratory. When these mouse heart cells are transplanted into left ventricles of damaged mouse hearts, they engraft and differentiate into mature cardiomyocytes that function like normal adult heart cells.

Scientific Abstract:
BACKGROUND: Cardiovascular progenitor cells (CPCs) have been identified within the developing mouse heart and differentiating pluripotent stem cells by intracellular transcription factors Nkx2.5 and Islet 1 (Isl1). Study of endogenous and induced pluripotent stem cell (iPSC)-derived CPCs has been limited due to the lack of specific cell surface markers to isolate them and conditions for their in vitro expansion that maintain their multipotency. METHODOLOGY/PRINCIPAL FINDINGS: We sought to identify specific cell surface markers that label endogenous embryonic CPCs and validated these markers in iPSC-derived Isl1(+)/Nkx2.5(+) CPCs. We developed conditions that allow propagation and characterization of endogenous and iPSC-derived Isl1(+)/Nkx2.5(+) CPCs and protocols for their clonal expansion in vitro and transplantation in vivo. Transcriptome analysis of CPCs from differentiating mouse embryonic stem cells identified a panel of surface markers. Comparison of these markers as well as previously described surface markers revealed the combination of Flt1(+)/Flt4(+) best identified and facilitated enrichment for Isl1(+)/Nkx2.5(+) CPCs from embryonic hearts and differentiating iPSCs. Endogenous mouse and iPSC-derived Flt1(+)/Flt4(+) CPCs differentiated into all three cardiovascular lineages in vitro. Flt1(+)/Flt4(+) CPCs transplanted into left ventricles demonstrated robust engraftment and differentiation into mature cardiomyocytes (CMs). CONCLUSION/SIGNIFICANCE: The cell surface marker combination of Flt1 and Flt4 specifically identify and enrich for an endogenous and iPSC-derived Isl1(+)/Nkx2.5(+) CPC with trilineage cardiovascular potential in vitro and robust ability for engraftment and differentiation into morphologically and electrophysiologically mature adult CMs in vivo post transplantation into adult hearts.